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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
B 3357 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/03218	11/05/1999	11/05/1998
International Patent Classification (IPC) or national classification and IPC C12N15/13		
Applicant MICROMET GMBH et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22/11/1999	17.08.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Armandola, E Telephone No. +49 89 2399 7493

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/03218

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-72 as originally filed

Claims, No.:

1-54 as received on 17/07/2000 with letter of 17/07/2000

Drawings, sheets:

1/19-19/19 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 2, 12-15, 16 (partially), 17-29, 39 (partially), 40-43.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 2, 12-15, 16 (partially), 17-29, 39 (partially), 40-43 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4, 5, 7-9, 11, 32-38, 39 (partially), 50-54
	No:	Claims	1, 3, 6, 10, 16 (partially), 30, 31, 44-49
Inventive step (IS)	Yes:	Claims	4, 5, 7-9, 11, 50, 51
	No:	Claims	1, 3, 6, 10, 16 (partially), 30-38, 39 (partially), 44-49, 52-54
Industrial applicability (IA)	Yes:	Claims	1, 3-11, 16, 30-39, 44-54
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 2, 12-15, 16 (partially), 17-29, 39 (partially), were not examined as their subject-matter is not sufficiently characterized. Additional comments can be found in Item VII, iv).

Claims 40-43 were not examined as they refer to a compound which is not identified by any structural or functional feature which makes a meaningful comparison with the prior art possible. The subject-matter of the claims might encompass a known compound, already used for the purpose described in the claim by, but which could not have been identified based on the present characterization.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 98 15579 A (CANTERBURY HEALTH LIMITED ;HART DEREK NIGEL JOHN (NZ)) 16 April 1998 (1998-04-16)

D2: TUTING T. ET AL. : 'AUTOLOGOUS HUMAN MONOCYTE-DERIVED DENDRITIC CELLS GENETICALLY MODIFIED TO EXPRESS MELANOMA ANTIGENS ELICIT PRIMARY CYTOTOXIC T CELL RESPONSES IN VITRO: ENHANCEMENT BY COTRANSFECTION OF GENES ENCODING THE TH1-BIASING CYTOKINES IL-12 AND IFN-ALPHA.', J. Immunol. , 01. February 1998, vol. 160, no. 3, pages 1139-1147

D2 was not listed in the ISR, a copy of the document is annexed to this report.

D1 discloses an antibody specific for dendritic cells and a method to isolate dendritic cells by using this antibody.

D2 discloses the transfection of dendritic cells with plasmids encoding melanoma antigens and cytokines (IL-12, TNFα) to enhance their ability to elicit an immune response.

Novelty (Art. 33(2) PCT)

Claims 1, 3, 6, 10, 16 (partially), 30, 45-47 and 49 cannot be considered novel in view of document D1 which discloses an antibody selectively binding to dendritic cells but not to freshly isolated PBMCs (see D1, p.12, line 31 to p. 13, line 3 and p.16, lines 8-11) through the antigen CMRF-56, a method for preparing the antibody, cells producing the antibody, modifications of the antibody with a detectable moiety, a method of isolating DCs with the antibody, a kit and compositions containing the antibody.
The antibody of D1 is reported to also bind a subpopulation of CD19+ lymphocytes only upon culture of T-cell depleted PBMC for 16 h.
The formulation of Claim 1 does not define the antibody for which it seeks protection in terms that are sufficiently clear to distinguish it from the disclosure of D1 because, in general, under the definition PBMCs are intended freshly isolated cells unless otherwise indicated. Therefore, the skilled person reading Claim 1 and trying to understand the extent of protection conferred by the claim, would first interpret it as excluding antibodies reacting with both DCs and freshly isolated PBMCs.
The antibody disclosed in D1 reacts with DCs, does not react with freshly isolated PBMCs, but reacts with a CD19+ subpopulation of cultured PBMCs.
The decision whether the antibody defined in Claim 1 differs from the antibody of D1 is, therefore, left open to the reader's interpretation and understanding of the term PBMCs.
The objection to lack of novelty could, however, be overcome, if the antibody of Claim 1 were defined not in terms of the result to be achieved, as is presently the case, but in terms of precise functional and/or structural features that might clearly distinguish it from the prior art, such as the detailed phenotype of the cells it recognizes, the epitope it recognizes, the hybridoma it is secreted by or/and its amino acid and/or nucleotide sequence.

Claim 31 is not considered novel because DCs displaying features of immature and/or mature DCs from PBMCs are known (as described in the application) as are DCs recognized by the antibody of Claims 1-3 and 6 (see D1).

Claim 44 is not considered novel because any known transgenic (or non-transgenic)

animal comprises the dendritic cells of Claim 31 or the T cells obtainable by method 33 or 35.

Claim 48 is not considered novel because T cells which can be used for adoptive immunotherapy are known. The fact that they are obtained by a new method does not render the T cells novel in comparison with any antigen specific T-cell which can be isolated by any other method.

Claims 4, 5, 8, 9 and 11 can be considered novel because an antibody recognizing a DC subpopulation which is $CD64^-$, $CD33^+$, $CD45RA^+$, $CD11c^+$, $p55^-$ and $CD16^+$ has not been described in the prior art.

Claims 7, 50 and 51 can be considered novel because it refers to a bispecific antibody recognizing both an epitope on DCs and one on another cell type. Such a bispecific antibody has not been disclosed in the prior art.

Claims 32-38, 39 (partially) and 52-54 can be considered novel because the well known methods described in the claims have never been applied in the prior art to DCs that are recognized by an antibody specific for DCs not recognizing PBMCs, and such DCs, although described in D1, were not modified to express a recombinant nucleic acid molecule.

Inventive step (Art. 33(4) PCT)

Claims 32-39 and 52-54 are not considered to entail an inventive step because the methods described in the claims are known to the person skilled in the art as standard methods in the immunological field and can be easily applied to any DC subpopulation, not only to the DC described in the application.
With particular reference to Claim 52, D2 discloses the modification of dendritic cells with (among other) IL-12 and IFN-α, the technique described in D2 can be applied also to the DCs of Claim 1 without the exercise of inventive skills.

Re Item VIII
Certain observations on the international application

Clarity (Art. 6 PCT)

i) Claim 2 is not clear because the maturational stage between immature and mature DCs is not clearly defined by technical features such as, for example, the surface antigens expressed by such a population. In view of the heterogeneity of DC subpopulations the skilled person would be in doubt as to how to identify the DC subpopulation of the claim. DCs isolated from different organs display different (sometimes overlapping) surface markers. Simply defining DCs as "...of a maturational stage between immature and mature DCs." id not sufficient to indicate which features the DCs falling within the scope of the claim should display. The markers indicated in Figure 8 of the application represent only one of the possible combinations of surface molecules that might be used to define DCs in an intermediate stage of maturation, the claim as formulated encompasses all of these combinations, but not all of them may be recognized by the antibody of Claim 1.

ii) In Claim 5 the wording "...are of restricted size and granularity located between lymphocytes and monocytes." is not clear in that it does not specify how size and granularity are determined and leaves the skilled person in doubt as to the means by which the DCs of the claim should be classified.
In "Rick W., Klinische Chemie und Mikroskopie, 6th ed., 1990, p. 48-49", for example, size and granularity are determined my light microscopy. While it is clear how to distinguish cells of a size intermediate between lymphocytes and monocytes, it is not clear how the corresponding granularity could be determined. Table 16 on page 49 shows that granules can be present or absent in lymphocytes and monocytes and their appearance can be "fine" or "very fine", what may be "located between" these definitions is unclear.
Form reading the description it seems more likely that the wording of Claim 5 refers to the determination of size and granularity by light scatter display in FACS; if this is the case, clarification of the claim in this sense would be appropriate.

iii) In Claims 6, 17, 23 and 29 the terms "fragment" and "derivatives" without any structural or functional limitation are considered to be vague and unclear as they leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the scope of the claims unclear and open to interpretation.

iv) Claims 12-15, 16, 17-29, 39, 44 are not clear because their subject-matter is not sufficiently characterized.

According to Rule 6.3 PCT, an invention should be defined in terms of its essential technical features. The antigen of Claim 12 is defined by the feature of being recognized by the antibody of Claims 1-9, which has, in turn, been identified as recognizing an antigen on a certain subclass of dendritic cells. This circular argument does not allow to unambiguously identify the antigen and to exclude that the antigen might be known. Therefore, while the antibody might be novel, the antigen could be known but not yet detected on DCs. Further characterizing features of the claimed antigen that are necessary for the definition of the invention, such as its amino acid sequence, should be included in the claim.

Claim 13-15, 17-29 and 45 are not clear because the polynucleotides for which protection is sought are not identified by any structural feature. The skilled person would not know how to identify the polynucleotide encoding the antibody of Claims 1-7, (which is only generally identified as recognizing a certain DC subpopulation) among all the polypeptides which could code for such an antibody. Such antibody may be constituted by any combination between heavy and light chains which, in turn, are coded for by nucleic acids whose sequence is the result of recombination and mutation events. It would, therefore, be impossible for the skilled person to precisely identify the nucleic acid(s) for which protection is sought among all the possible molecules which might fulfill the requirements of the claim, without a more precise characterization through structural features, such as their nucleic acid sequence.

In addition, while antibody specificity might be determined by one variable region domain only, it is often the combination of specific heavy and light chains and of two or more domains on them, which determines the recognition pattern of an antibody. Antibodies may share one or more domains, and still have a different specificities. Therefore, the subject-matter of Claims 13-15, 17-29 and 45 may not be novel as it encompasses nucleic acid molecules encoding variable regions or isolated domains of known antibodies which are shared by the antibody interacting with the antigen on the specific DC subpopulation described in the application, without having a specificity related to this antigen. For example, a nucleic acid sequence encoding an antibody (e.g. a single chain antibody) with the same light chain of the antibody described in Claims 1-7 but with a greatly different heavy chain, which determines its antigenic specificity, would also fall within the scope of the claims. As mentioned above for an antigen, also for a DNA further characterizing features are necessary for the definition of the invention, such as its DNA sequence.

As a consequence also those parts of Claims 16, 31, 39, 44, 46, 47 referring to the above mentioned claims are not clear.

The skilled person can easily derive the DNA encoding an antibody, as long as he/she is provided with the hybridoma producing the antibody or at least with an antigen that would allow him/her to produce a mAb specific for that antigen with reasonable expectation of success. In this sense, only the antibodies of Claims 8 and 9 are sufficiently characterized to allow the cloning of the DNA encoding them without undue burden of experimentation.

v) Claims 31 and 32 regard dendritic cells. In their formulation the claims encompass cells which are part of a human body. The attention of the applicant is drawn to the fact that, should the application enter the regional phase before the EPO, such a claim would not fulfill the requirements of Art. 52(2) and Rules 23c (a) and 23e (1).
Moreover, the DCs of the claims are vaguely defined, making reference to claims which define an antibody which is also very vaguely defined.